CHRONIC MICROELECTRODE RECORDING ARRAYS

Quarterly Report

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CHRONIC MICROELECTRODE RECORDING ARRAYS

Executive Summary

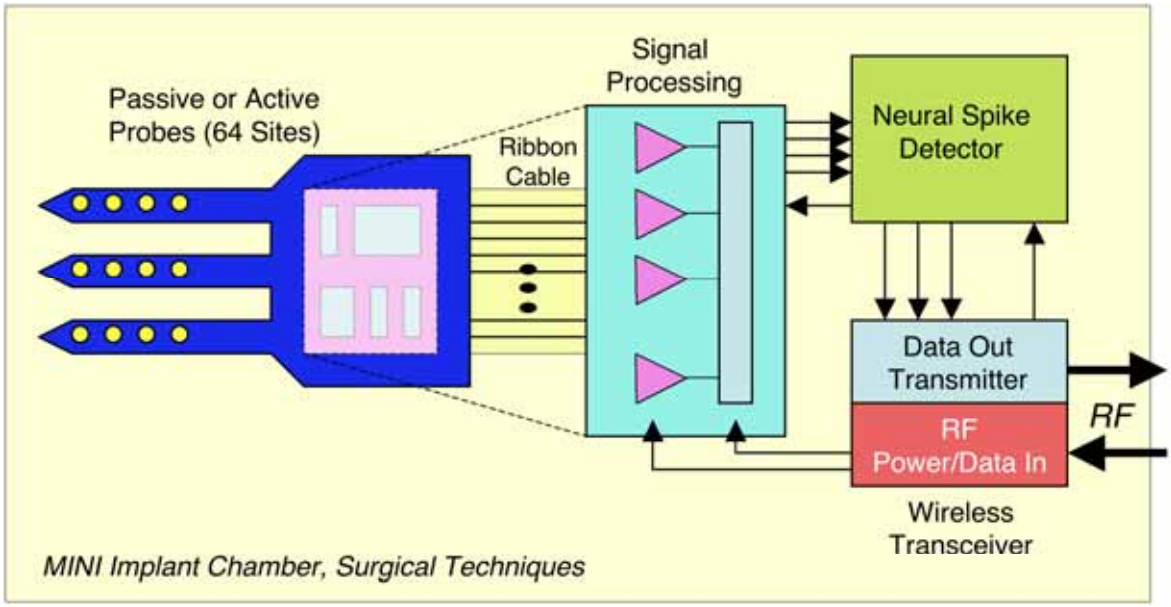
This contract seeks to develop wireless microsystems for chronic multi-channel recording in the motor cortex of primates, setting the stage for subsequent trials in quadriplegic humans. The approach we are taking uses active or passive multi-channel two-dimensional silicon probes containing 16-64 sites each, arranged in three-dimensional arrays. The probe output signals are routed to circuitry on the rim of the implant assembly using multi-lead silicon- or polymer-based microcables. The rim-mounted circuitry identifies neural spikes and passes the spike occurrences to the outside world over a bidirectional wireless link that derives power and control signals for the implant from an externally-supplied RF carrier. The implanted circuitry can also be used to output a full analog representation of the neural activity on any single site.

During the past quarter, inputs, we made substantial progress on the components required fro the cortical microsystem. We successfully tested two versions of an implantable amplifier chip for use with passive probes and iterated the design. The revised 16-channel amplifier chip is now in fabrication. We also completed testing the 8-channel version of our spike detector chip along with most portions of our wireless chip. Both work as expected. The entire analog signal chain consisting of a 16-channel passive probe, amplifier chip, neural spike detector, and wireless interface chip was assembled, tested, and operated successfully in recording from rat cortex. This was a very significant milestone in the development of the intended microsystem.

We also successfully completed fabrication and most testing of the non-multiplexed version of our active probe during the past term. The full 32-channel version of our neural processing unit (spike detector) was designed and is now in fabrication. The MINI implant housing went through significant iteration during the past quarter to make it easier and more effective to implant. We also began exploring a subcutaneous implant assembly as a possible alternative for the final system.

Activity Summary

During the past quarter, we have continued to work on the various components that will be required to realize wireless implants of 64 recording sites in primate motor cortex. The target microsystem is shown below, and consists of the recording probes, a silicon or polymeric cable, signal selection and amplification (on the probe chip or on the implant rim, a neural spike detector to separate the spikes from background noise and digitize them, and a wireless interface chip which transmits data out and derives power and command signals from an external RF system.



During the past quarter, the following activities went forward:

- Our latest results were presented at the Neural Interfaces Workshop in Bethesda in September. A paper on our work also appeared in the September issue of the *IEEE Engineering in Medicine and Biology Magazine*.

- Fabrication was completed on our 64-site non-multiplexed CMOS recording probes, designed for use with our analog spike detector. These probes are still in test but all testing to date has indicated that they are fully functional. The probes have enhanced self-test capabilities as compared with earlier designs.

- A 32-channel version of our Neural Processing Unit was designed and is now in fabrication at MOSIS. The chip allows two such processors to be used in parallel to service 64 parallel data channels in scan mode.

- The wireless interface for these probe assemblies has been fabricated and is now in test. All indications are that the chip is fully functional.

- The full analog signal path, from a 16-channel passive probe (with parylene ribbon cable), per-channel amplifiers, spike detectors, and wireless interface (up to the antenna) has been operated successfully.

- The system housing and printed circuit board were re-designed, manufactured and tested. Several modifications to the design were made to address issues that have arisen during previous *in vivo* experiments. The housing size was reduced by 60% from MINI 4.5.

- The recent MINI designs are now machined out of titanium and housed with two 51-pin connectors and six bonded probes. The system is designed to be populated with six chronic passive electrode arrays (96 channels total).

- *Materials:* The new versions of the system housing have been machined out of commercially pure titanium, grade 2. This material was chosen on the basis of its relative ease to machine, but more importantly its known biocompatibility.

- *In-vitro* testing: Bench-top tests were performed to test and characterize the electrical viability of each electrode site. Impedance data, including magnitude and phase for each site was collected and logged.

- *In-vivo* testing: Ongoing *in-vivo* tests were performed in monkeys. One primate implant procedure was completed at the University of Pittsburgh. The focus of this procedure was to continue to develop the surgical techniques, continue to evaluate the design of the housing and the recent modifications made from the previous iteration.

- Design is underway for a new set of passive probes. These probes have the same site and shank configurations as the last mask set. They differ from the last designs in that they have cables that come off at right angles to lower their profile and facilitate closure of the dura over the implant. There are two general classes of designs: 3D devices with cables that are on the platform and 2D devices with parylene bending regions.

- The MINI implant housing has continued to be the focus of implant experiments in primates; however, we have also begun to explore a subcutaneous implant assembly for the final system. It should simplify both the packaging of the electronics and the actual surgery.

Each of these areas is discussed in the following section.

Research Results and Discussion

Probe Development

During the past quarter, the discrete amplifier circuit chips have been thoroughly characterized both in-vitro and in-vivo. These allow the use of the entire microsystem with passive probes. The 16-channel amplifier chip, submitted for fabrication to MOSIS in March 2005, performs very well in acute experiments. A schematic of this amplifier design for a single channel is shown in Fig. 1. For chronic use however, it was necessary to make a few modifications.

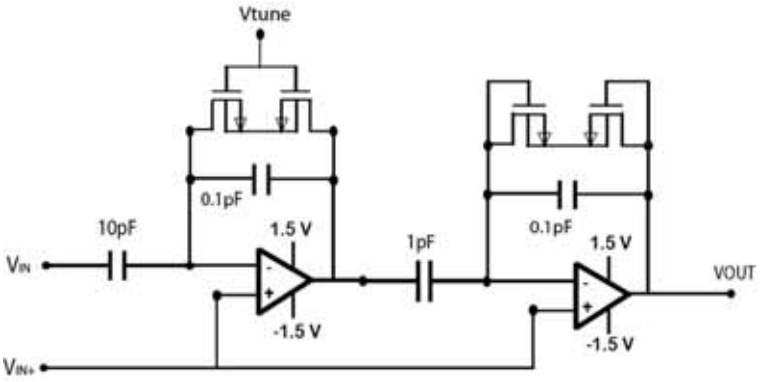


Fig. 1: Schematic of the amplifier design (single channel) fabricated at MOSIS in Spring 2005.

The non-inverting input terminal to the amplifier, Vin+, can be used to null the DC output offset voltage, which is unavoidable and is caused by the fabrication process. This is important so that the amplified signal is not saturated at the output due to the DC offset. In this design of two cascaded amplifiers, providing a total gain of 60dB, the two non-inverting terminals were connected together. Trying to null the final output offset voltage with just one control line posses a problem since the two amplifiers may need opposite input polarities to be nulled. Indeed, this was the case encountered during testing. The other issue here was that the external voltage needed for Vin+ cannot be provided in chronic applications.

These problems were addressed and version 2 of the amplifier chip, which was submitted to MOSIS in September 2005. The modifications include separating the non-inverting inputs and including an on-chip bias with fuses to set the DC voltages. Three voltage dividers were included to set the operating DC voltage of Vtune, Vin+_1 and Vin+_2. A test chip was also included to determine the required DC voltages to be fixed on the working amplifiers. Figure 2 shows the layout of the second version of the 16-channel amplifier chip. The dimensions of this chip are 1.2mm x 1.8mm (version 1 chip measured 1.6mm x 2.2mm).

Also included on this MOSIS run is an alternative design for the amplifier. This design meets all the specifications for this application and eliminates the need to cascade the two amplifiers. The advantage of this design is to provide more immunity to process

variations; it uses a single input offset voltage to null the output offset. It also includes a voltage to tune the low-frequency cutoff and on-chip bias generation. It was also expected to be more compact; however, the overall 16-channel chip size is actually comparable to the cascaded-amplifier design since a large feedback capacitance is needed. This chip measures 1.2mm x 1.9mm, and its layout is shown in Fig. 3.

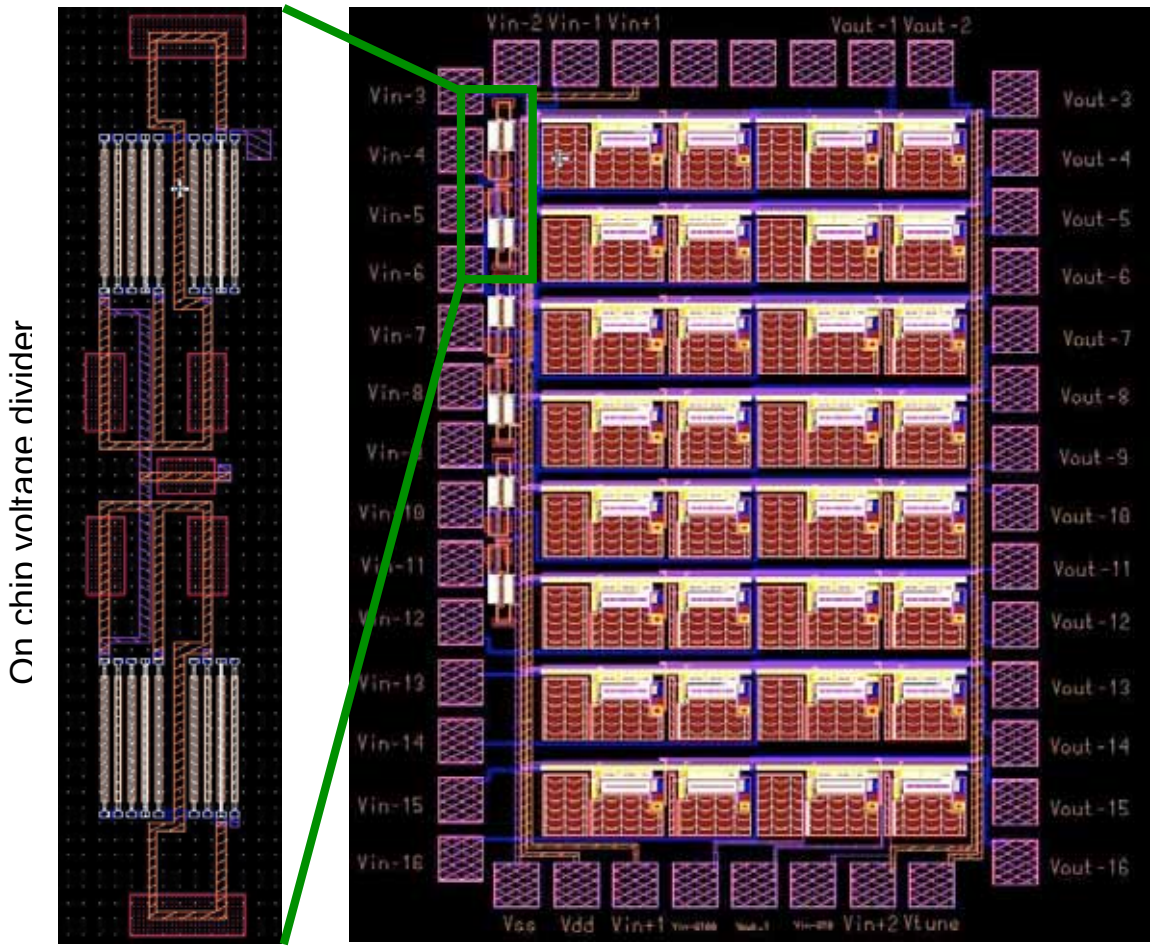


Fig. 2: Layout of the AMI 0.5µm 16-channel amplifier chip version 2 (submitted for fabrication in September 2005). Chip size: 1.2mm x 1.8mm.

Also during the past quarter, the first version of the system was integrated on a silicon platform. This platform included a 16-channel passive probe with an integrated parylene cable, a 16-channel amplifier chip, an 8-channel spike detector test chip and a telemetry chip. Each component was wire bonded to the platform and integrated using lithographically defined gold interconnections. Figure 4 shows a picture of the first version of the system, which measures 1.6cm x 1.2cm. As shown in the picture, a connector was used for testing purposes. In-vivo testing was conducted in a rat to validate each of the chips. The system was validated up to the input of the transmitting antenna. The silicon platform for a 64-channel system has been designed, including four

16-channel passive probes, four 16-channel amplifier chips, two 32-channel neural processing unit (NPU) chips and a telemetry chip. The complete system is about the same size as the first version of the platform since the connector is eliminated. A schematic of this layout is shown in Fig. 5.

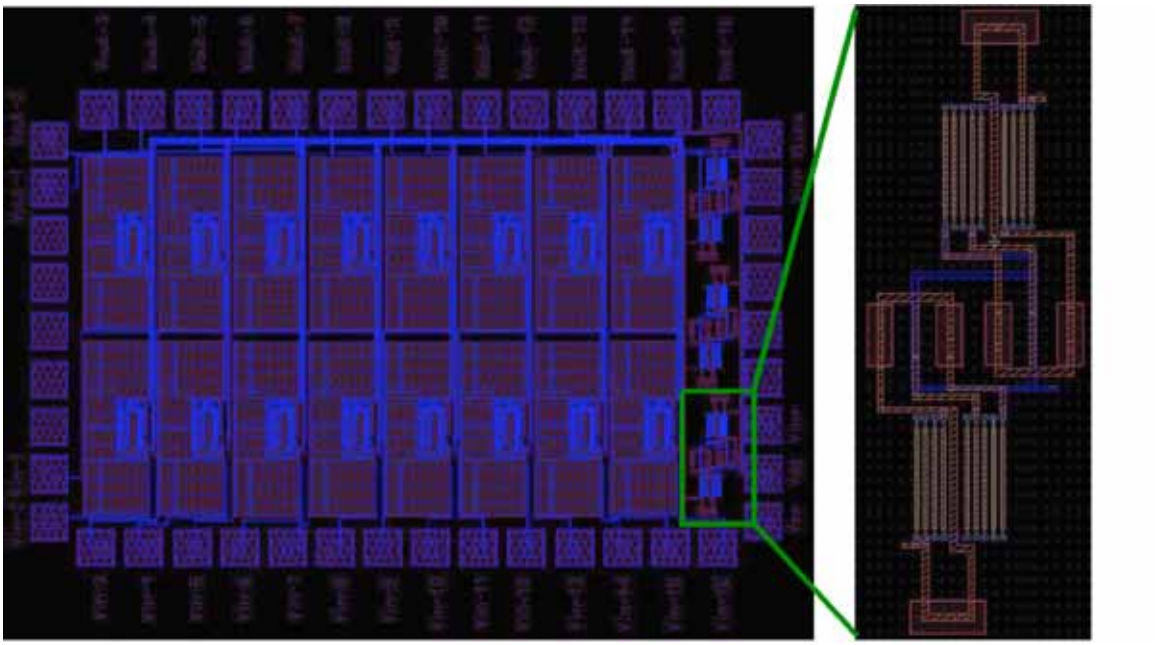


Fig. 3: Layout of the AMI 0.5µm 16-channel amplifier chip using a single amplifier design (submitted for fabrication in September 2005). Chip size: 1.2mm x 1.9mm.

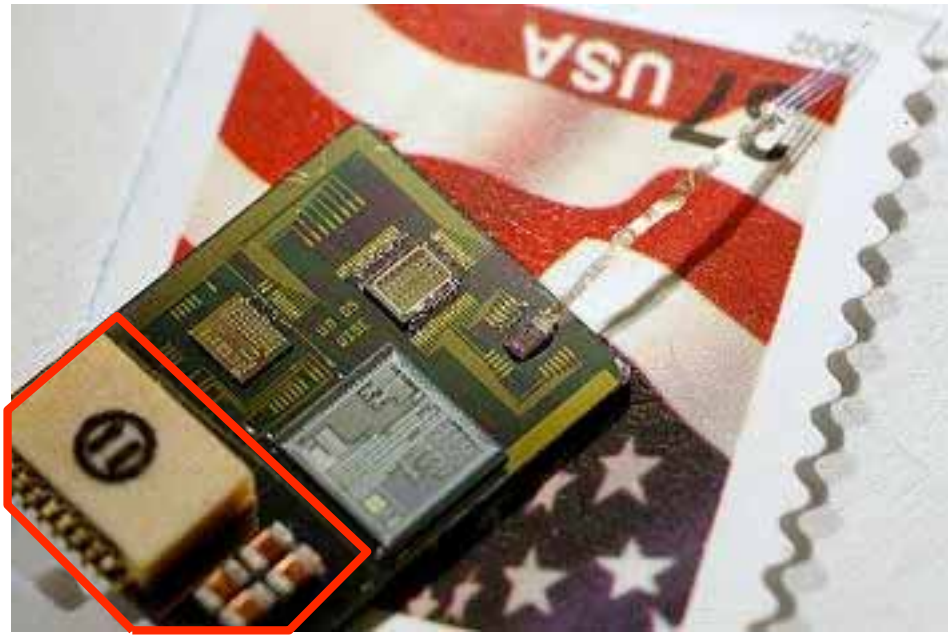


Fig. 4: First version of the complete microsystem integrated on a silicon platform, including a temporary connector used for testing.

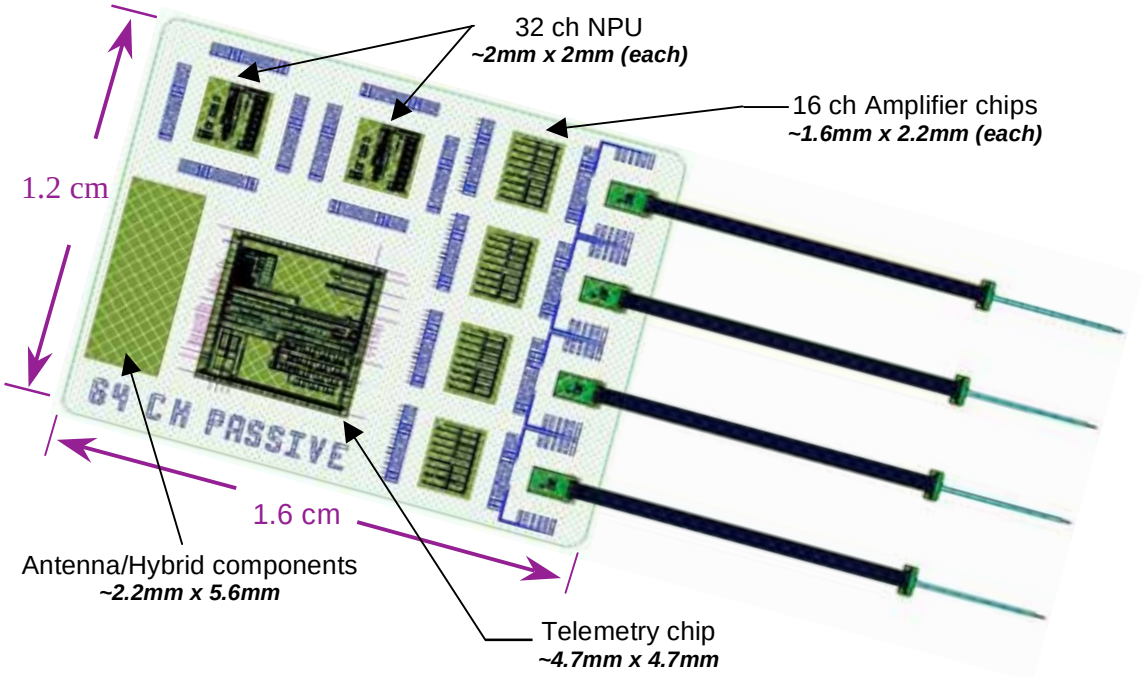


Fig. 5: Layout of a 64-channel system on a silicon platform.

During next quarter the new set of amplifier chips will be tested, the design for the platform will be finalized and fabricated, and the final system integration and in-vitro testing will take place before implantation into primates.

Bidirectional Recording Interface

- *Completion of tests on the 8-channel spike detector (SD-8)*

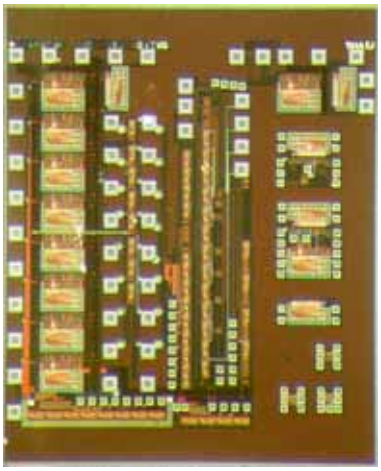


Fig. 6 shows the photograph of the SD-8 chip, fabricated in the AMI 0.5µm standard CMOS process. To evaluate the spike detector operation in response to real neural signals, pre-recorded neural signals that had already been band-pass filtered and amplified with a gain of 1000 (60dB) were applied, and the desired function was observed. Fig. 2 shows two selected waveforms resulting from in-vitro tests.

Fig. 6: Photograph of the 8-channel spike detector chip.

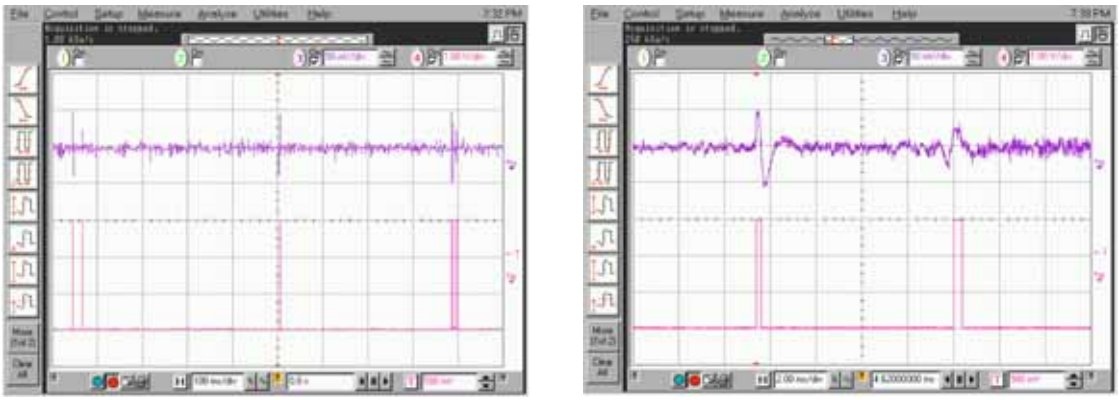


Fig. 7: In-vitro operation of the 8-channel spike detector using pre-recorded neural data.

The *Digital Data Processing* block, which is in charge of tagging the active channels with the associated addresses, storing the addresses in a local memory, and communicating with the external circuitry has also been tested. The input and output signals resulting from these experiments are shown in Fig. 8.

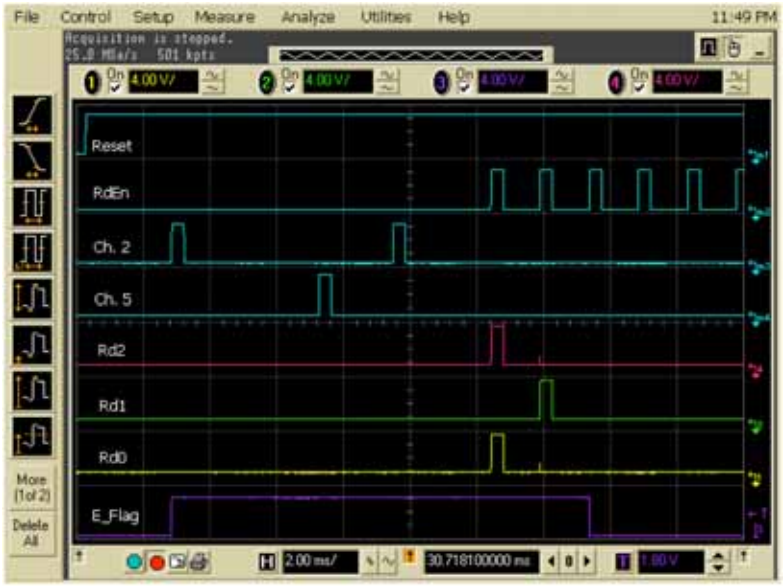
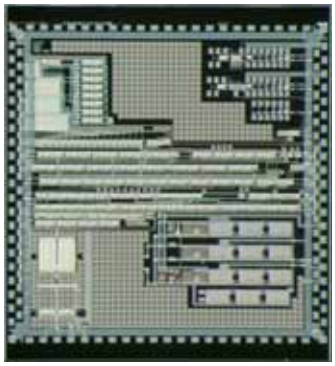


Fig. 8: Operation of the Digital Data Processing block on the SD-8



- *The Bidirectional Telemetry Test Chip (BTT)*

The fabricated BTT whose photo is shown in Fig. 9 has been partially tested. Again, the chip performs as expected although the input power module has not yet been tested. The external receiver for this telemetry link is also still in development.

Fig. 9: Die photo of the BTT

A few selected signals and waveforms resulting from the Controller and the Back Telemetry tests are shown in Fig. 10 and Fig. 11, respectively. The tests show correct operation from both of these circuit blocks.

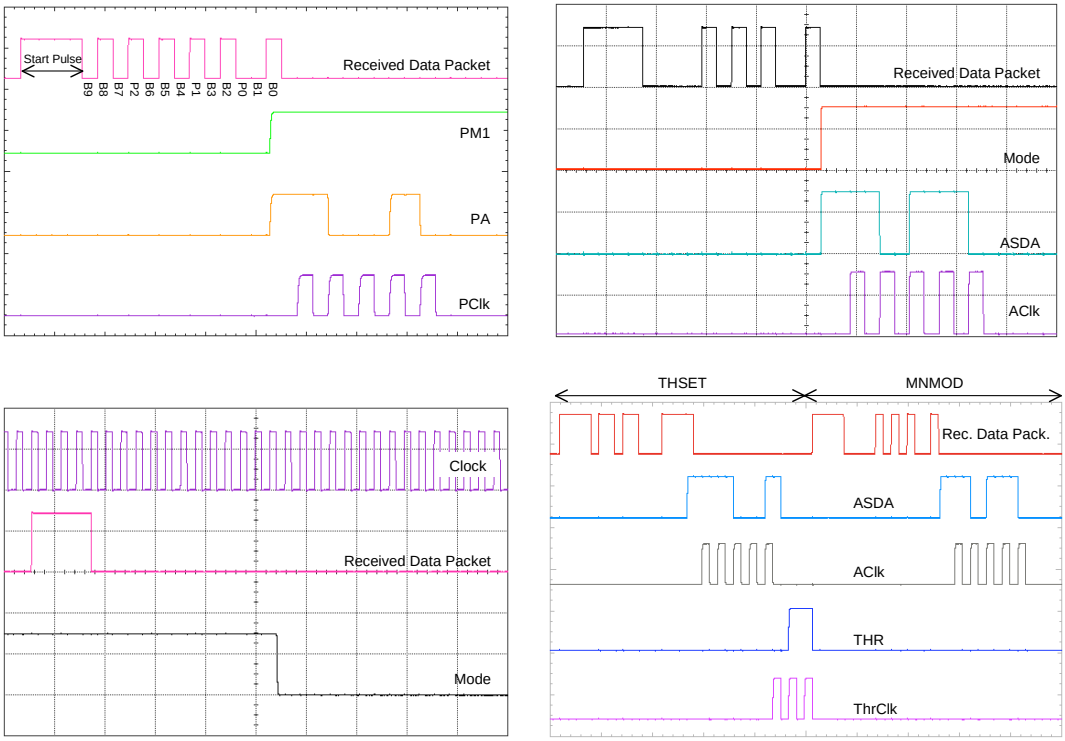


Fig. 10: Selected tests on the Controller implemented on BTT

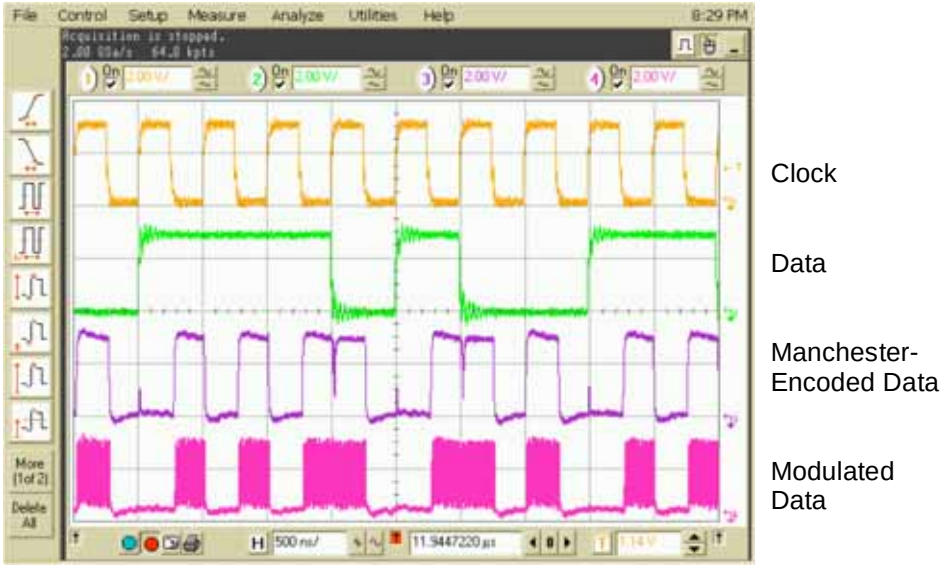


Fig. 11: Waveforms resulting from experiments on the Back Telemetry block.

Figure 11 shows the system clock, the neural data, the Manchester-encoded data/clock signal for transmission to the outside world, and the on-off keyed input to the implanted antenna.

- *In-Vivo Tests for the Single-Channel Prototype System*

To examine the operation of the fabricated building blocks, a single-channel prototype system was implemented on a silicon platform as noted above. The system (shown in Fig. 4) was used to record signals from rat cortex, and the spike detector was set to threshold on negative spikes. Fig. 12 shows an example of the recorded signals. The left figure shows the input (amplified) neural signal, the spike detector output, and the input to the antenna. The right figure shows the same information but on a expanded time scale.

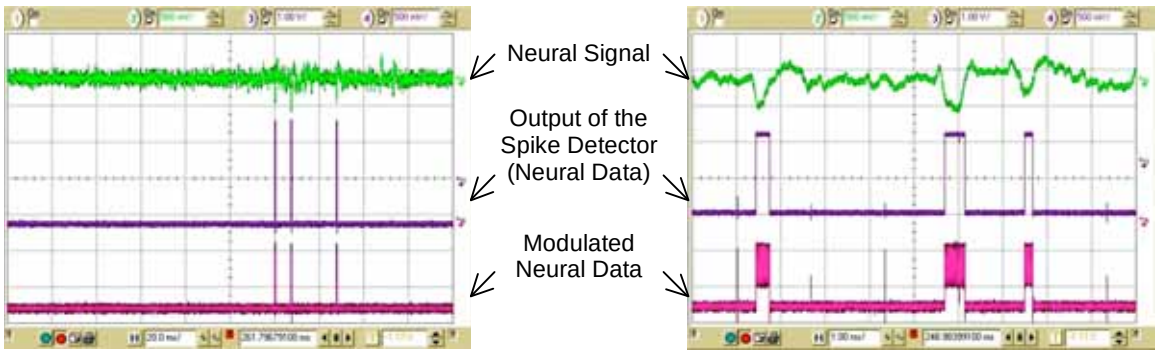


Fig. 12: Selected In-vivo Test Results

- *Completion of the NPU Design*

Considering some of the modifications and architectural optimizations on the NPU discussed last quarter, a design for the 32-channel NPU was completed, and the chip was submitted for fabrication. To be used in a basic system consisting of four 64x8 active probes, the NPU is operated in the Basic Mode; however, set in the Master-Slave Mode, two 32-channel NPUs can form a 64-channel NPU, which can handle the signals recorded by four 16-site passive probes. The layout of the 32-channel NPU is shown in Fig. 13.

Future Plans

During the coming quarter, the NPU will be fabricated. In the meantime, the rest of the BTT tests will be performed. If the BTT tests and measurements necessitate any kind of modification, the final version of the BTM will be designed and submitted to MOSIS for fabrication. We will also design, fabricate, and test the antennas required for the system as well as developing an external setup to support subsequent microsystem evaluation in the wireless mode.

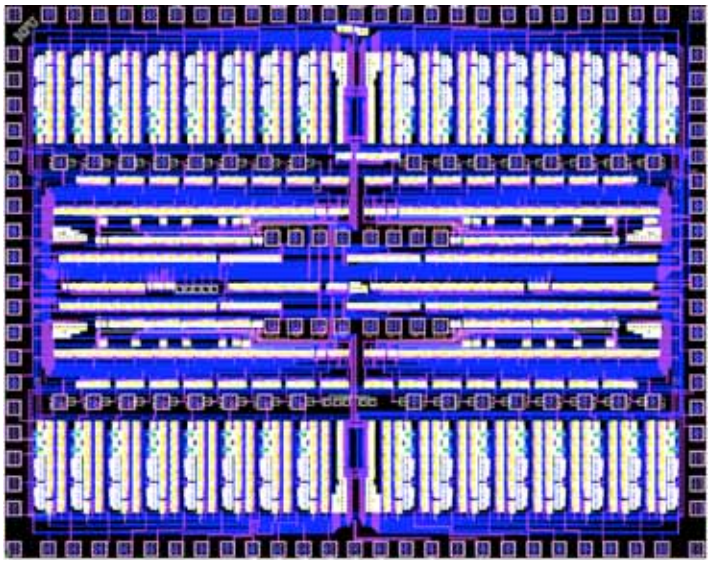


Fig. 13: Layout of the 32-channel NPU

Implant Assembly Development
Miniaturizing the MINI:

There were several major changes in this iteration. First and foremost, we were able to reduce the size of the MINI (5.1) by 60% (Fig. 14a). We also added 45° chamfers to the bottom edges of the MINI. These changes lowered the amount of overhanging material above the skull, eased the accessibility of the brain to MINI interface, and reduced leakage by creating a better seal at these interfaces.

Another large change was the replacement of the hand-made glass cover-slide lumen covers with a machined Plexiglas cover (Fig. 14b). These covers are still optically clear, permit visual inspection of the brain, hydrostatically seal the lumen, and in addition are replaceable and reduce the variability in the surgical procedure. The lumen is hydrostatically sealed with a silicone o-ring, which was injection-molded in-house and made to fit the lids exactly using a silicone elastomer material. Four tapped holes have been added to the housing design to accommodate threaded rods on which the lids would be slid. The rods also aid in securing the PCB board in place and give the new lumen covers a fixed location. It provides stability and a means to compress the o-rings by screwing on nuts to the tops of the lumen covers. It also permits the lids to be replaceable.

The bone screw attachments were placed on the sides that were parallel to the connectors rather than perpendicular to them. The cranium that corresponds to this region has a much lower grade of curvature reducing the distance between the bone screws and the MINI. The attachments are placed the minimal distance away from the walls thus minimizing the distance that must be spanned by the screws. Fluidic ports were incorporated into the sides of the MINI replacing the silicone ports. These reduced variability between surgeries and can be quickly and easily used incase of any problems

with leakage. The single screw that secures the lid onto the housing now allows the lid to be removed twice as fast and loss of the screws half as likely. The shape of the mating regions is now a cube. External torsional forces would then be distributed along the mating faces of the cube, preventing any rotation of the lid.

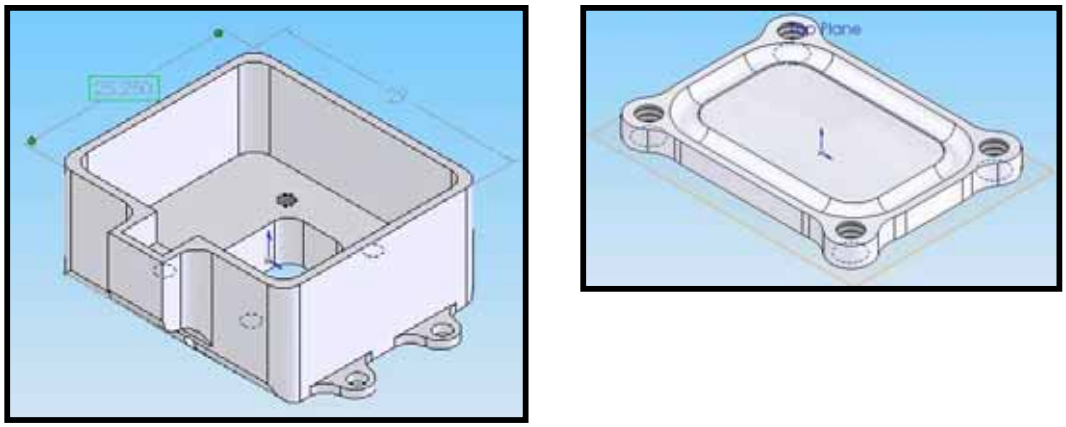


Fig. 14: (a) MINI 5.1 illustration, and (b) acrylic machined lumen cover.

Monkey Experiments Rationale

The latest designed chamber was manufactured, tested, and implanted in monkey parietal cortex at the University of Pittsburgh on Sept. 30 (Fig. 15a-f). The results of this procedure were very positive. Sixty-four channels (four 16-channel electrodes) were successfully implanted. The probe cables were suspended in aCSF enclosed in a hydrostatic lumen. Impedances immediately after surgical procedure showed all 64 channels were intact and electrically viable. High quality neural recordings were present on nearly all of the channels. At the time of this report (10 days post-op), recordings were qualitatively stable.

Exploring a Subcutaneous Implant Assembly

The present MINI design has some important advantages for prototyping the system. It contains the implant within the assembly and permits connectors to be well protected. It also seals the cranial surface so that connectors and electronics are protected from the in-vivo environment and it potentially allows the addition of electronics to a working implant by simply plugging a board containing the electronic system into the sockets of the working implant. However, such an arrangement does not result in a truly implantable system since the height of the unit will exceed 1cm. Thus, the wireless system is head-mounted, but not wireless as intended. In order to achieve a truly implantable system, we are exploring the implant arrangement shown in Fig. 16. Here, the circuit package is mounted on top of the skull under the skin, while cables lead to the implanted electrodes through an opening in the skull. The skull is removed over the implant area and then replaced. Low profile electrodes are being developed for this approach that will have no more than about 100μm of rise above the cortical surface. This assembly should make it much easier to perform the surgical implant and places the

implant over an undisturbed portion of the skull. The electronics are offset from the implant site, which may cut down on RF coupling into the recording channels. The electronics package here is one we know how to seal in vacuum and is of proven hermeticity. We have performed one mock implant of such as system and will assemble a full passive implant of this type during the next few weeks for further evaluation. It should be remembered that we are also developing a button version of the implant using active probes. This button geometry has the advantage of removing the cables but will require a higher rise above the cortex and a larger area over the cortex.

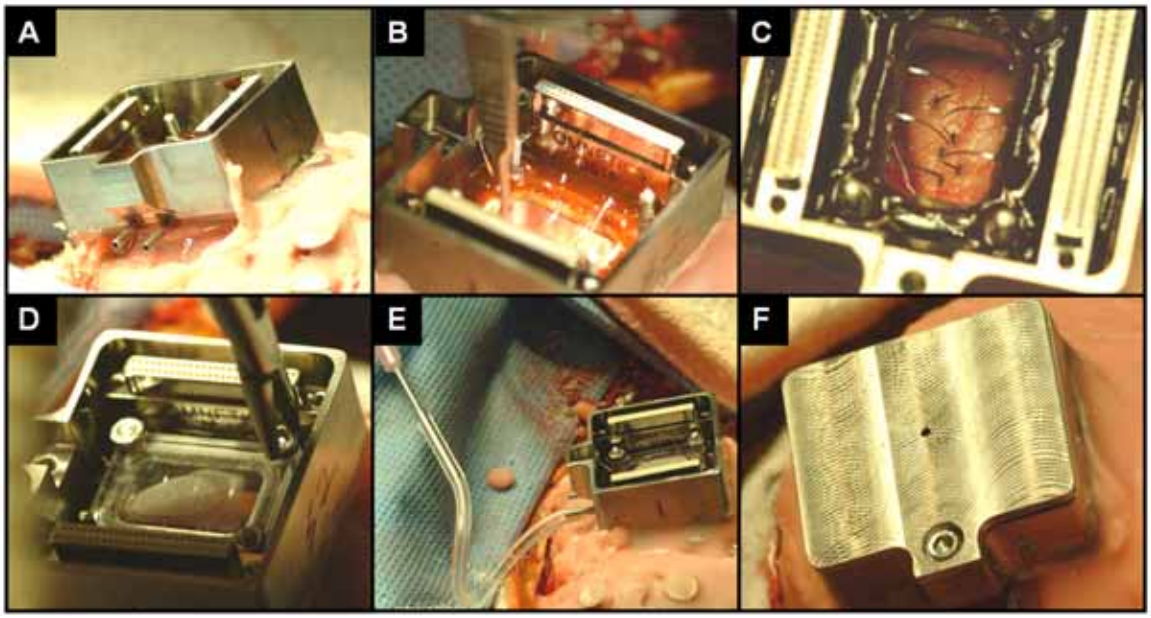


Fig. 15: Monkey 96-channel titanium chamber. (a) chamber mounted on skull with fluid I/O ports shown, (b) insertion of one 16-channel probe, (c) all probes inserted into cortex, (d) placement of acrylic lumen lid, (e) filling of inner lumen with aCSF, (f) chamber lid in place.

Conclusions

During the past quarter, inputs, we made substantial progress on the components required fro the cortical microsystem. We successfully tested two versions of an implantable amplifier chip for use with passive probes and iterated the design. The revised 16-channel amplifier chip is now in fabrication. We also completed testing the 8-channel version of our spike detector chip along with most portions of our wireless chip. Both work as expected. The entire analog signal chain consisting of a 16-channel passive probe, amplifier chip, neural spike detector, and wireless interface chip was assembled, tested, and operated successfully in recording from rat cortex. This was a very significant milestone in the development of the intended microsystem.

We also successfully completed fabrication and most testing of the non-multiplexed version of our active probe during the past term. The full 32-channel version of our neural processing unit (spike detector) was designed and is now in fabrication.

The MINI implant housing went through significant iteration during the past quarter to make it easier and more effective to implant. We also began exploring a subcutaneous implant assembly as a possible alternative for the final system.

All portions of the intended system have now been prototyped or are in fabrication; however, it is still uncertain if we can have a fully-operational microsystem in place by the end of the year as required by this contract. The MOSIS chips (amplifiers and NPU) will not even be returned from the foundry until December. If all components needed by this system had been straightforward and the proper approaches known, then developing and testing such a system during the base period of the contract would still have been heroic. But there are many areas where the proper approach to solving the problems confronting these systems is *not* known. Thus, the results of the first-pass system remain uncertain. Nevertheless, we intend to have this system operational by the end of 2005 if possible.

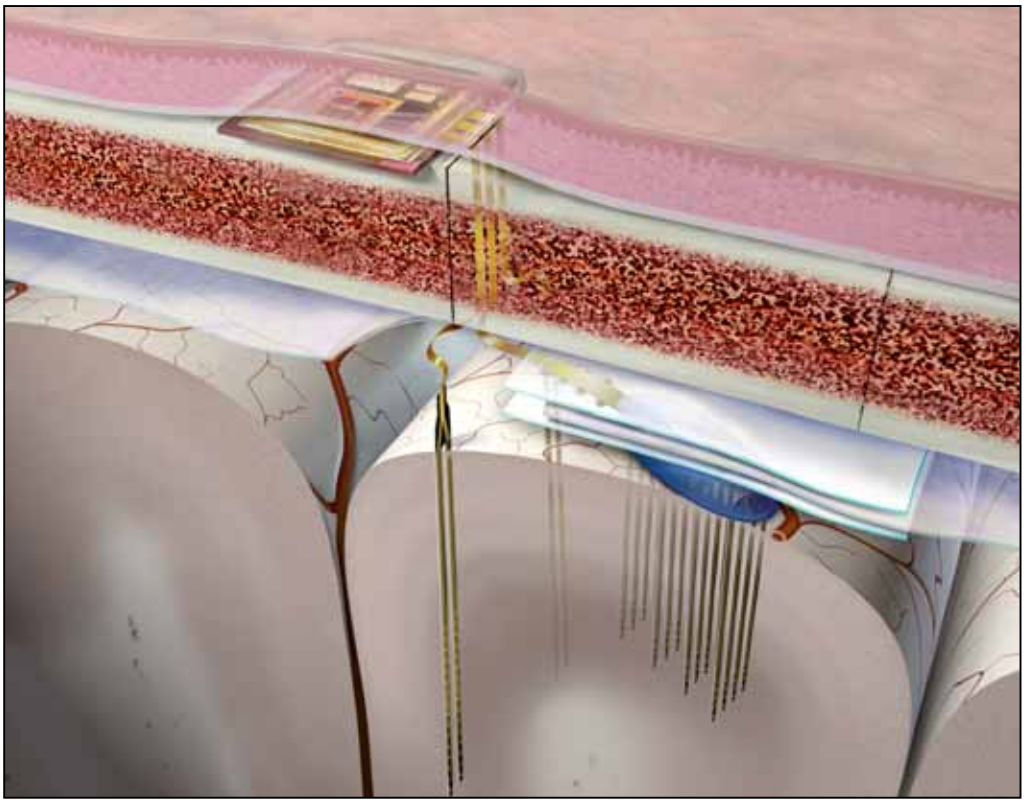


Fig. 16: Artist's sketch of a subcutaneous implant assembly for use in motor cortex.